

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of :

Applicants: **Tae-Woong Koo, et al.**

Application No.: 10/814,981

Filed: March 30, 2004

For: **METHOD TO DETECT MOLECULAR  
BINDING BY SURFACE-ENHANCED  
RAMAN SPECTROSCOPY**

Group Art Unit: 1614

Examiner: Do, Pensee T.

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Commissioner for Patents  
Post Office Box 1450  
Alexandria, Virginia 22313-1450

Sir:

Applicants respectfully request the consideration of this Appeal pursuant to 35 U.S.C. §134 from the Examiner's decision rejecting claims 1-34 as set forth in the January 12, 2006 Office Action.

The Commissioner is hereby authorized in this, concurrent and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2666 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17.

**I. Real Party in Interest.**

The Real Party in Interest is Intel Corporation, 2200 Mission College Blvd., Santa Clara, CA, assignee of the inventors' entire interest.

**II. Related Appeals and Interferences.**

None.

**III. Status of the Claims.**

Claims 1-16 and 19-34 stand finally rejected and are the subject of this Appeal.

Claims 17 and 18 are cancelled.

**IV. Status of Amendments.**

In an Advisory Action dated June 7, 2006 the examiner indicated that Applicants' proposed Amendments after Final would not be entered.

**V. Summary of Claimed Subject Matter.**

Embodiments of the invention are directed to detecting binding events between molecules using Raman spectroscopy. The methods are useful for detecting binding between biomolecules, such as antibodies to antigens, and receptors to ligands. The two molecules involved in the binding event are referred to specific binding pair members.

A Raman spectrum, similar to an infrared spectrum, consists of a wavelength distribution of bands corresponding to the molecular vibrations of the sample being analyzed (the analyte). To obtain a Raman spectrum, typically a beam from a light source, such as a laser, is focused on the sample generating inelastically scattered radiation which is optically collected and directed into a wavelength-dispersive spectrometer. Although Raman scattering is a relatively low probability event, surface-enhanced Raman spectroscopy (SERS) can be used to enhance signal intensity in the resulting vibrational spectrum. Enhancement techniques make it possible to obtain as much as a  $10^6$  to  $10^{14}$  fold Raman signal enhancement. Typically, metal surfaces, especially those of small metal particles, have been found to be active toward enhancing Raman signals. Further enhancements are obtained through the addition of salts such as lithium chloride.

A SERS signal is used to detect a molecular binding event by first associating a specific binding pair member with a SERS-active particle or substrate and detecting a Raman signal. The second specific binding pair member is contacted with the first specific binding pair member and the Raman signal from the first molecule is detected. Binding is detected by detecting a change in the SERS signal from the first specific binding pair member: the signal obtained before binding is compared to the signal obtained after binding. A Raman spectrum of a specific binding pair member is measured before binding and the Raman spectrum of that binding specific binding pair member is again measured after binding. These two signals are subtracted and if a difference is found in the signal from the specific binding pair member before and after the contact with a potential binding partner has occurred, a binding event has been detected.

Table 1 provides a listing of independent claims and separately argued dependent claims. References to the specification are provided for the claims in Table 1.

**Table 1**

<b>Claim</b>	<b>Specification Reference</b>
<p>1. A method to detect binding of a first specific binding pair member to a second specific binding pair member, comprising:</p> <p style="padding-left: 40px;">a) associating a first specific binding pair member with a surface-enhanced Raman scattering-active particle or substrate;</p> <p style="padding-left: 40px;">b) contacting the first specific binding pair member associated with the surface-enhanced Raman scattering -active particle or substrate with a second specific binding pair member; and</p> <p style="padding-left: 40px;">c) detecting binding of the second specific binding pair member to the first specific binding pair member by detecting a</p>	<p>Figure 1; Paragraphs: [007], [0010], [0032] [0035]</p>

<p>difference in a surface-enhanced Raman scattering signal of the first specific binding pair member before contacting the first specific binding pair member with the second specific binding pair member and after contacting the first specific binding pair member with the second specific binding pair member, wherein the surface-enhanced Raman scattering signal is generated by excitation of the first specific binding pair member associated with the surface-enhanced Raman scattering-active particle or substrate, thereby detecting binding of the first specific binding pair member to the second specific binding pair member.</p>	
<p>12. The method of claim 11, wherein the chemical salt is lithium chloride.</p>	<p>Figure 1; Paragraphs: [007], [0010], [0032] [0035], [0055]</p>
<p>21. The method of claim 20, wherein the surface-enhanced Raman scattering-active substrate comprises a porous silicon substrate comprising impregnated metals.</p>	<p>Figure 1; Paragraphs: [007], [0010], [0032] [0035], [0064-0067]</p>
<p>22. A method to detect binding of an antibody, or fragment thereof, to an antigen, comprising:</p> <ul style="list-style-type: none"> <li>a) immobilizing an antibody on an immobilization substrate;</li> <li>b) contacting the immobilized antibody with a metal particle to adsorb the immobilized antibody on the metal particle;</li> <li>c) contacting the immobilized antibody with an antigen; and</li> <li>d) detecting binding of the antigen to</li> </ul>	<p>Figure 1, Figure 3, Paragraphs [007], [0010], [0017], [0018], [0053], [0058], [0064-0067]</p>

<p>the antibody, or fragment thereof, by detecting a difference in a surface-enhanced Raman scattering signal generated by the antibody before contacting the antibody with the antigen and after contacting the antibody with the antigen, wherein the surface-enhanced Raman scattering signal is generated by excitation of the surface-enhanced Raman scattering-active particle or substrate, thereby detecting binding of the antibody to the antigen.</p>	
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<p>26. A method to detect an analyte in a biological sample, comprising:</p> <ul style="list-style-type: none"> <li>a) immobilizing a first specific binding pair member on a surface, wherein the first specific binding pair member binds the analyte;</li> <li>b) contacting the immobilized first specific binding pair member with a metal particle to adsorb the immobilized first specific binding pair member on the metal particle;</li> <li>c) contacting the immobilized first specific binding pair member adsorbed on the metal particle with the biological sample; and</li> <li>d) detecting a surface-enhanced Raman scattering signal generated by excitation of the metal particle absorbed by the immobilized first specific binding pair member before contacting the immobilized first specific binding pair member with the second specific binding pair member and after contacting the first specific binding pair member with the second specific binding pair member, wherein a difference in the detected surface-enhanced Raman scattering signals is indicative of the presence of the analyte in the biological sample.</li> </ul>	<p>Figure 1, Paragraphs [007], [0010], [0017], [0018], [0053], [0058], [0064-0067]</p>
<p>29. The method of claim 26, wherein the first specific binding pair member is adsorbed on the metal particle in the presence of lithium chloride.</p>	<p>Figure 1; Paragraphs: [007], [0010], [0032] [0035], [0053], [0055], [0058], [0064-0067]</p>

<p>31. A method to detect an antibody or a fragment thereof, comprising:</p> <p style="padding-left: 40px;">a) immobilizing the antibody, or fragment thereof, on a surface;</p> <p style="padding-left: 40px;">b) contacting the antibody, or fragment thereof, with a metal particle to adsorb the immobilized antibody on the metal particle; and</p> <p style="padding-left: 40px;">c) detecting a surface-enhanced Raman scattering signal generated by excitation of the metal particle absorbed by the immobilized antibody, or fragment thereof, thereby detecting the antibody, or fragment thereof.</p>	<p>Figure 1, Figure 3, Paragraphs [007], [0010], [0017], [0018], [0053], [0058], [0064-0067]</p>
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## VI. Grounds of Rejection to be Reviewed on Appeal.

The grounds of rejection for review are:

(1) claims 1-16 and 19-25 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention,

(2) claims 1-4, 6-11, 13-16, and 20 stand rejected under 35 U.S.C. §102(b) as unpatentable over Tarcha et al. (U.S. Patent No. 5,376,556),

(3) claim 12 stands rejected under 35 U.S.C. §103(a) as unpatentable over Tarcha et al. in view of Fray (U.S. Patent No. 4,904,356),

(4) claim 21 stands rejected under 35 U.S.C. §103(a) as unpatentable over Tarcha et al. in view of Gole et al. (U.S. Patent No. 6,589,883),

(5) claims 5, 22-28, 30, and 31-34 stand rejected under 35 U.S.C. §103(a) as unpatentable over Tarcha et al. in view of Maine et al. (U.S. Patent No. 6,221,619), and

(6) claim 29 stands rejected under 35 U.S.C. §103(a) as unpatentable over Tarcha et al. in view of Maine et al. and further in view of Fray.

## VII. Argument.

### A. Rejections Under 35 U.S.C. §112, Second Paragraph.

#### *i. Argument for claims 1-16 and 19-21*

The Examiner has stated that the limitation in claims 1 and 22, “the surface-enhanced Raman scattering signal,” is unclear because “[t]here are two signals being monitored, one before the second specific binding pair member is added and another signal after binding” and it is unclear which signal is meant. Applicants traverse this rejection as it applies to claims 1 and 22 and the claims dependent therefrom.

The Federal Circuit has stated that “[t]he operative standard for determining whether this requirement [§112, second paragraph] has been met is ‘whether those skilled in the art would understand what is claimed when the claim is read in light of the specification.’” See Beachcombers, International v. WildeWood Creative Products, Inc., 31 U.S.P.Q.2d 1653 (Fed. Cir. 1994). On its face, the claim states that the SERS signal at issue is that of the first specific binding pair member that is associated with a SERS active particle or substrate. Additionally, the specification explains that the SERS effect is associated with the first specific binding pair member when the first specific binding pair member is positioned close to the SERS-active particle or surface. See, e.g. Specification [0035]. As a result of contact between the first specific binding pair member that is in such close proximity to the SERS-active particle or surface, and the second specific binding pair member, the SERS signal associated with the first binding pair member is changed. This change in SERS signal associated with the first binding pair member, when detected, is indicative of binding between the first and second binding pair members. See Specification [0032]. Therefore what is monitored is a change in the SERS effect associated with the first specific binding pair member. See Figure 1.

The meaning of the phrase when read in light of the specification would be clear to one of skill in the art because the skilled artisan would know that one signal is monitored, i.e., the SERS signal associated with the first specific binding pair member. Because one of skill in the art would understand the metes and bounds of the phrase, Applicants believe that the Examiner’s § 112 rejection should be reversed.

#### *i. Argument for claims 22-25*

The Examiner has stated that the limitation in claims 1 and 22, “the surface-enhanced Raman scattering signal,” is unclear because “[t]here are two signals being

monitored, one before the second specific binding pair member is added and another signal after binding” and it is unclear which signal is meant. Applicants traverse this rejection as it applies to claims 1 and 22 and the claims dependent therefrom.

Applicants’ argument with respect to claims 22-25 is similar to the argument for claims 1-16 and 19-21. Applicants assert that one of skill in the art would understand the claim when read in light of the specification. Independent claim 22 states that the signal to be monitored by Raman spectroscopy is that of an immobilized antibody absorbed on a metal particle. It is the difference in the signal from the adsorbed antibody before and after binding that is monitored by generating a surface-enhanced Raman scattering signal through excitation of the antibody-particle association

The meaning of the phrase when read in light of the specification would be clear to one of skill in the art because the skilled artisan would know that one signal is monitored, i.e., the SERS signal associated with the immobilized antibody. Because one of skill in the art would understand the metes and bounds of the phrase, Applicants believe that the Examiner’s § 112 rejection should be reversed.

**B. Rejections Under 35 U.S.C. §102(b) as Unpatentable over Tarcha et al.**

*i. Argument for claims 1-4, 6-11, 13-16, and 20*

The examiner has rejected claims 1-4, 6-11, 13-16, and 20 as anticipated by Tarcha et al. (U.S. Pat. No. 5,376,556; “Tarcha”). However, it is essentially axiomatic in patent law that in order for a reference to be anticipatory of a claim, it must disclose all the elements of the claim. Helifix Ltd. V. Blok Lok, Ltd., 208 F.3d 1339 (Fed. Cir. 2000). As stated in claim 1, the a binding event between a first and second specific binding pair member is observed “by detecting a difference in a surface-enhanced Raman scattering signal of the first specific binding pair member.” The difference measured is the comparison of the Raman signal from the first specific binding pair member before and after contacting the first specific binding pair member with the second specific binding pair member. The specification states, “[b]y detecting binding of a first specific binding pair member to a second specific binding pair member, methods disclosed herein allow detection of molecular interactions between a first molecule and a second molecule. Methods described herein can be used to detect interaction between virtually any molecules provided that one of the molecules generates a detectable SERS signal when associated with a SERS-active particle or substrate, and this SERS signal is affected by

binding of the first molecule to the second molecule. For example, in one aspect, the first specific binding pair member is an antibody and the second specific binding pair member is an antigen that is specifically bound by the antibody. In another aspect, a first specific binding pair member is a receptor and a second specific binding pair member is a ligand.” Specification, Para [0010]. Further, no labels are necessary: “[t]he methods disclosed herein do not require the labeling process of traditional fluorescent assays, such as immunoassays, used for detecting binding of a first biomolecule to a second biomolecule. Since labels are not used and/or fluorescent detection is not employed, the background signal of an assay is greatly reduced.” Specification, Para [007].

Tarcha does not disclose monitoring binding events by observing the SERS spectrum of a binding pair member itself. Instead, what Tarcha does disclose is monitoring the Raman signal from a Raman-active label molecule. In the specification, Tarcha defines a Raman-active label molecule as “any substance which produces a detectable Raman spectrum, which is distinguishable from the Raman spectra of other components present.” Tarcha, col.10:ll.19-23. Tarcha further distinguishes the Raman-active label molecule from the specific binding member with the following definition directed to the specific binding member as a species distinct from the label: “‘Specific binding member,’ as used herein, is a member of a specific binding pair, i.e., two different molecules where one of the molecules, through chemical or physical means, specifically binds to a second molecule.” Tarcha, col.10: ll33-53. All assays are performed in Tarcha in the presence of a label molecule having a detectable Raman spectrum. The SERS spectra obtained in Tarcha are of the label molecule. See for example, Figure 3 in Tarcha. In Figures 3A, 3B and 3C, respectively, the SERRS spectrum observed for a Raman-active label, HABA (2-[4-hydroxyphenylazo]benzoic acid), and the SERRS spectrum for the label bound to a specific binding member, avidin, are compared to the spectrum of avidin alone. The Figure notes, “[n]o discernable spectrum was observed in this region from surface absorbed avidin in the absence of HABA.” Tarcha, col.7:ll.21-27; Col.19:ll.12-14. Thus in Tarcha, where no label is associated with a specific binding member, no discernable spectrum is observed. Tarcha measures differences in spectra from Raman-active labels, not differences in spectra from specific binding members, since “no discernable spectrum” is observed from specific binding members.

Therefore Applicants traverse this rejection as it applies to claim 1 and the claims dependent from claim 1. Reversal of the Examiner's rejection is sought.

C. Rejections Under 35 U.S.C. §103(a) as Unpatentable over Tarcha et al. in view of Fray

i. *Argument for claim 12*

Claim 12 stands rejected under 35 U.S.C. §103(a) as unpatentable over Tarcha et al. in view of Fray (U.S. Patent No. 4,904,356, "Fray"). The burden of proof in establishing a prima facie case of obviousness under § 103 rests with the Patent Office. In re Piaskeki, 745 F.2d 1468, 1472 (Fed. Cir. 1984).

A prima facie case of obviousness requires, in part, that all the elements of a claim be found in the references cited for the obviousness rejection. However, neither Tarcha nor Fray disclose monitoring a difference in surface-enhanced Raman scattering signal for a specific binding pair member as stated in claim 1, the claim from which claim 12 depends. As discussed in Section VII.B.i. above, Tarcha discloses monitoring spectra obtained from label molecules associated with specific binding members, not from a specific binding pair member itself. In fact, Tarcha reports in Figure 3C that "no discernable spectrum was observed... from surface absorbed avidin [a specific binding member] in the absence of HABA [a Raman-active label]." Tarcha, col.7:ll.21-27; Col.19:ll.12-14.

In addition, Fray does not disclose monitoring a difference in surface-enhanced Raman scattering signal for a specific binding pair member. Fray is deficient in many respects. For example, Fray does not disclose any of the following concepts from claim 1: specific binding between molecules, obtaining Raman spectra, associating a molecule with a Raman-active particle or surface, obtaining a surface-enhanced Raman spectrum, or monitoring a difference in a surface-enhanced Raman spectrum for a molecule before and after a binding event. What Fray does disclose is something far different: "an electrode for use in electro-refining of metals, ... a cell including the electrode and ... an electrorefining and an electrowinning method using the cell." Fray col.1:ll.6-9.

Further, the examiner has cited Fray because "Tarcha fails to teach the chemical salt is lithium chloride" stating that, "Fray teaches using lithium chloride salt as a salt of a metal surface to be refined." However, in order to be used as reference in an

obviousness rejection Fray must be analogous art. In re Deminski, 796 F.2d 436 (Fed. Cir. 1986). A two step test is applied to determine whether a reference is analogous art: (1) whether the reference is within the inventor's the field of endeavor; and (2) if not, whether the reference is reasonably pertinent to the particular problem with which the inventor was involved." Not only is there is no disclosure at all of spectroscopy let alone SERS in Fray, there is also no disclosure of monitoring binding between molecules. Fray does not qualify as a reference that is within the inventors' field of endeavor even under a broad definition of a field of endeavor such as Raman spectroscopy, let alone a more narrow one such as SERS spectroscopy or detection of molecular binding using Raman spectroscopy. Fray relates to "an electrode for use in electro-refining of metals and has nothing to do with spectroscopy or molecular detection of any kind. In fact, the words "Raman," "spectroscopy," "molecular," and "detection" are not once mentioned in Fray. Further, even if Fray were within the inventor's field of endeavor, it is not reasonably pertinent to the problems of enhancing weak Raman signals and detecting molecular binding events. Fray relates to electrochemical techniques and electrorefining of metals, not spectroscopy or molecular detection. Electrorefining is unrelated to Raman detection techniques and one of skill in the art would not have reason to believe that methods or principles useful in electrorefining would have anything to do with achieving Raman signal enhancement. Thus, Applicants submit that Fray is not a reference that is available for use in an obviousness rejection because Fray is non-analogous art.

Further, in establishing a prima facie case, the Patent Office must show that (1) the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention and (2) that the prior art would have revealed a reasonable expectation of success. In re Viak, 947 F.2d 488, 493 (Fed. Cir. 1991). "[P]articular findings must be made as to the reason a skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." In re Kotzab, 217 F.3d 1365, 1371 (Fed. Cir. 2000). Further, in relying on the knowledge of persons of ordinary skill in the art, the Patent Office must "explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination." In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Without objective evidence to combine references, it is inferred that the references were selected with the assistance of

hindsight. Id. The use of hindsight to simply recite elements gleaned from various references is not a satisfactory obviousness rejection.

There no teaching or suggestion to use lithium chloride as an enhancer for SERS in Fray or in Fray in combination with Tarcha. Although Fray does mention lithium chloride and metal (as cited by the Examiner: Fray, Col.1:ll.27-40), there is no reference to Raman spectroscopy, molecular detection, or that one would expect an enhancement in SERS signal through the use of lithium chloride in conjunction with a metal surface. The fact that lithium chloride is used in Fray in electrochemical methods (apparently as an “impurity” or “diluent” and because “halide salts” are usually “cheaper,” Fray, Col.1:ll.30-38) such as electro-refining and electrowinning does not in any way imply that it might also be prove useful in obtaining enhancements in a Raman spectrum of a molecule.

Thus, for the foregoing reasons, that Tarcha and Fray fail to disclose all the elements of claim 12, that Fray is non-analogous art, and that there is no motivation to combine Tarcha and Fray in the art, Applicants believe that the Examiner’s § 103 rejection of claim 12 should be reversed.

D. Rejections under 35 U.S.C. §103(a) as unpatentable over Tarcha et al. in view of Gole et al.

*i. Argument for claim 12*

Claim 21 stands rejected under 35 U.S.C. §103(a) as unpatentable over Tarcha et al. in view of Gole et al. (U.S. Patent No. 6,589,883, “Gole”). The burden of proof in establishing a prima facie case of obviousness under § 103 rests with the Patent Office. In re Piaskeki, 745 F.2d 1468, 1472 (Fed. Cir. 1984).

A prima facie case of obviousness requires, in part, that all the elements of a claim be found in the references cited for the obviousness rejection. However, neither Tarcha nor Gole disclose monitoring a difference in surface-enhanced Raman scattering signal for a specific binding pair member as stated in claim 1, the claim from which claim 12 depends. As discussed in Section VII.B.i. above, Tarcha discloses monitoring spectra obtained from label molecules associated with specific binding members, not from a specific binding pair member itself. In fact, Tarcha reports in Figure 3C that “no discernable spectrum was observed... from surface absorbed avidin [a specific binding member] in the absence of HABA [a Raman-active label].” Tarcha, col.7:ll.21-27;

Col.19:ll.12-14. Similarly, Gole is silent as to SERS and monitoring molecular binding events by Raman spectroscopy.

Further, the Examiner states that Tarcha fails to teach that the SERS active substrate is a porous silicon substrate comprising impregnated metals. However, in order to be used as reference in an obviousness rejection Gole must be analogous art. In re Deminski, 796 F.2d 436 (Fed. Cir. 1986); See also, Section VII.C.i.. Gole is not reasonably within the field of endeavor of the present invention. Gole's technical field, that of methods for enhancing and stabilizing photoluminescence of porous silicon substrates, is far removed from the field of molecular binding events and molecular detection by surface-enhanced Raman spectroscopy. Gole states, "[h]igh surface-area substrates formed in wafer scale through etching display a visible photoluminescence (PL) upon excitation (PLE) with a variety of visible and ultraviolet light sources. This room temperature luminescence has attracted considerable attention primarily because of its potential use in the development of silicon-based optoelectronics, displays, and sensors." Gole, col.1:ll.31-34.

Further, there is no teaching or suggestion to use the porous silicon or the metallized substrate of Gole to monitor the changes in a SERS spectrum of a molecule as a result of a binding event. In fact, Gole is silent as to monitoring binding events between molecules and generating a surface-enhanced Raman spectrum of a binding pair member. Further, there would be no reasonable expectation of success using the substrates of Gole as substrates for generating an enhanced Raman signal. In spectroscopic measurement and detection techniques in general, emission from a substrate is considered unwanted background noise and it to be avoided. A substrate is a carrier for the molecule to be detected or possibly a vehicle for enhancing the signal observed from the analyte being monitored. A signal from a substrate generally would interfere with and make detection of the signal from the analyte more difficult. Thus, a person of skill in the art would not be motivated to combine the teachings of Gole, those of optimizing photoluminescence from a substrate, with the teachings of Tarcha, those of detecting a Raman signal from a label molecule.

As stated above, the use of hindsight to simply recite elements gleaned from various references is not a satisfactory obviousness rejection. Thus, for the foregoing reasons, that Tarcha and Gole fail to disclose all the elements of claim 21, that Gole is non-analogous art, that there is no motivation to combine Tarcha and Gole, and that

there would be no reasonable expectation of success with the use of Gole's substrate to detect enhanced Raman signals, Applicants believe that the Examiner's § 103 rejection of claim 21 should be reversed.

E. Rejections under 35 U.S.C. §103(a) as unpatentable over Tarcha et al. in view of Maine et al.

*i. Argument for claims 5, 22-28, 30, and 31-34*

Claims 5, 22-28, 30, and 31-34 stand rejected under 35 U.S.C. §103(a) as unpatentable over Tarcha et al. in view of Maine et al. (U.S. Patent No. 6,221,619, "Maine"). The remarks distinguishing Tarcha from the current invention apply equally here. See Section VII.C.i. The Examiner indicates that Tarcha fails to teach immobilizing the first specific binding pair member/antibody on an immobilizing substrate. The Examiner relies upon the disclosure of Maine for different assay formats comprising attaching an antibody/antigen to a solid phase such as porous, non-porous materials, latex particles, microparticles, beads, membranes, microtiter wells, and plastic tubes. However, Maine is silent with regard to generating a surface-enhanced Raman scattering signal that is generated by excitation of a first specific binding pair member associated with the surface-enhanced Raman scattering active particle or substrate. Thus, since Maine and Tarcha fail to disclose all the elements in claim 1, the proposed combination would not have lead one of skill in the art to the method of the present invention. Applicants believe that the Examiner's § 103 rejection of these claims should be reversed

F. Rejections under 35 U.S.C. §103(a) as unpatentable over Tarcha et al. in view of Maine et al. and further in view of Fray

*i. Argument for claim 29*

Claim 29 stands rejected under 35 U.S.C. §103(a) as unpatentable over Tarcha et al. in view of Maine and further in view of Fray. The remarks distinguishing Tarcha from the current invention apply equally here. See Section VII.C.i. The Examiner indicates that Tarcha and Maine fail to teach that the first specific binding pair is adsorbed on the metal particle in the presence of lithium chloride. Therefore, the Examiner relies on Fray for the use of lithium chloride salt. However, for reasons stated above, that the combinations of Tarcha and Maine and Tarcha and Fray fail to disclose

all the elements of the claim, that there is no teaching or suggestion to combine Fray with Tarcha (or Maine), and that Fray is non-analogous art, Applicants request that the Examiner's rejection be reversed.

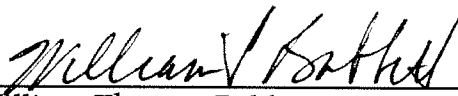
For the foregoing reasons, Examiner's rejections of claims 1-16 and 18-34 should be reversed.

If necessary, the Commissioner is hereby authorized in this, concurrent and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2666 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17, particularly extension of time fees.

Respectfully submitted,

BLAKELY, SOKOLOFF, TAYLOR, & ZAFMAN LLP

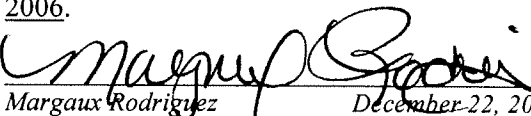
Dated: December 22, 2006.

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## VIII. Claims Appendix.

1. (Amended) A method to detect binding of a first specific binding pair member to a second specific binding pair member, comprising:
  - a) associating a first specific binding pair member with a surface-enhanced Raman scattering-active particle or substrate;
  - b) contacting the first specific binding pair member associated with the surface-enhanced Raman scattering -active particle or substrate with a second specific binding pair member; and
  - c) detecting binding of the second specific binding pair member to the first specific binding pair member by detecting a difference in a surface-enhanced Raman scattering signal of the first specific binding pair member before contacting the first specific binding pair member with the second specific binding pair member and after contacting the first specific binding pair member with the second specific binding pair member, wherein the surface-enhanced Raman scattering signal is generated by excitation of the first specific binding pair member associated with the surface-enhanced Raman scattering-active particle or substrate, thereby detecting binding of the first specific binding pair member to the second specific binding pair member.
2. The method of claim 1, wherein the surface-enhanced Raman scattering-active particle or substrate associated with the first specific binding pair member is a metal particle.
3. The method of claim 2, wherein the first specific binding pair member is associated with the metal particle by adsorbing the first specific binding pair member to the surface-enhanced Raman scattering surface.
4. The method of claim 3, wherein the metal particle comprises colloidal silver or gold.
5. The method of claim 3, wherein the first specific binding pair member is immobilized on an immobilization substrate prior to associating with the surface-enhanced Raman scattering-active surface.

6. The method of claim 1, wherein the difference in the surface-enhanced Raman scattering signal is a decrease in the signal.
7. The method of claim 6, wherein binding of the second specific binding pair member to the first specific binding pair member dissociates the first specific binding pair member from the metal particle.
8. The method of claim 1, wherein the difference in the surface-enhanced Raman scattering signal is an increase in the signal.
9. The method of claim 3, wherein adsorption is detected before the second specific binding pair member is contacted with the first specific binding pair member.
10. The method of claim 9, wherein adsorption is detected by detecting an increase in a surface-enhanced Raman scattering signal generated by the first specific binding pair member after contacting the first specific binding pair member with the metal particle.
11. The method of claim 3, wherein the first specific binding pair member is associated with the metal particle in the presence of a chemical salt.
12. The method of claim 11, wherein the chemical salt is lithium chloride.
13. The method of claim 1, wherein the first specific binding member is a protein and the second specific binding pair member is a protein.
14. The method of claim 13, wherein the first or second specific binding pair member is an antibody molecule, or fragment thereof.
15. The method of claim 1, wherein the first specific binding pair member is a receptor and the second specific binding pair member is a ligand.

16. The method of claim 1, wherein the first or second specific binding pair member is a nucleic acid molecule and the other of the first or second specific binding pair member is a protein.

17-18 (cancelled)

19. The method of claim 18, wherein surface enhanced coherent anti-Stokes Raman spectroscopy is used to detect the first specific binding pair member.

20. The method of claim 1, wherein the first specific binding pair member is associated with the surface-enhanced Raman scattering-active particle or substrate by immobilizing the first specific binding pair member on a surface-enhanced Raman scattering-active substrate.

21. The method of claim 20, wherein the surface-enhanced Raman scattering-active substrate comprises a porous silicon substrate comprising impregnated metals.

22. (Amended) A method to detect binding of an antibody, or fragment thereof, to an antigen, comprising:

- a) immobilizing an antibody on an immobilization substrate;
- b) contacting the immobilized antibody with a metal particle to adsorb the immobilized antibody on the metal particle;
- c) contacting the immobilized antibody with an antigen; and
- d) detecting binding of the antigen to the antibody, or fragment thereof, by detecting a difference in a surface-enhanced Raman scattering signal generated by the antibody before contacting the antibody with the antigen and after contacting the antibody with the antigen, wherein the surface-enhanced Raman scattering signal is generated by excitation of the surface-enhanced Raman scattering-active particle or substrate, thereby detecting binding of the antibody to the antigen.

23. The method of claim 22, wherein the antibody, or fragment thereof, is a whole antibody molecule.

24. The method of claim 22, wherein the antibody, or fragment thereof, is a Fab fragment.
25. The method of claim 22, wherein the metal particle comprises colloidal gold or silver.
26. (Amended) A method to detect an analyte in a biological sample, comprising:
- a) immobilizing a first specific binding pair member on a surface, wherein the first specific binding pair member binds the analyte;
  - b) contacting the immobilized first specific binding pair member with a metal particle to adsorb the immobilized first specific binding pair member on the metal particle;
  - c) contacting the immobilized first specific binding pair member adsorbed on the metal particle with the biological sample; and
  - d) detecting a surface-enhanced Raman scattering signal generated by excitation of the metal particle absorbed by the immobilized first specific binding pair member before contacting the immobilized first specific binding pair member with the second specific binding pair member and after contacting the first specific binding pair member with the second specific binding pair member, wherein a difference in the detected surface-enhanced Raman scattering signals is indicative of the presence of the analyte in the biological sample.
27. The method of claim 26, wherein the first specific binding pair member is an antibody, or fragment thereof.
28. The method of claim 26, wherein the metal particle comprises colloidal gold or silver.
29. The method of claim 26, wherein the first specific binding pair member is adsorbed on the metal particle in the presence of lithium chloride.
30. The method of claim 26, wherein the biologic sample comprises serum.
31. (Amended) A method to detect an antibody or a fragment thereof, comprising:
- a) immobilizing the antibody, or fragment thereof, on a surface;

b) contacting the antibody, or fragment thereof, with a metal particle to adsorb the immobilized antibody on the metal particle; and

c) detecting a surface-enhanced Raman scattering signal generated by excitation of the metal particle absorbed by the immobilized antibody, or fragment thereof, thereby detecting the antibody, or fragment thereof.

32. The method of claim 30, wherein the antibody, or fragment thereof, is a whole antibody molecule.

33. The method of claim 30, wherein the antibody, or fragment thereof, is a Fab fragment.

34. The method of claim 30, wherein the metal particle comprises colloidal gold or silver.

**IX. Evidence Appendix.**

No submissions.

**X. Related Proceedings Appendix.**

None.